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Studies on Bone Markers and Bone Mineral Density in Patients with Chronic Renal Failure

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Renal osteodystrophy has become a frequent complication in patients with chronic renal failure (CRF), and various histologic forms such as high turnover, low turnover and mixed bone disease have been demonstrated. The only reliable method for distinguishing patients with high turnover from those with low turnover bone disease is bone histomorphometric study, but its clinical utility is restricted. Because of its invasive nature, efforts have been made to predict indirectly the type and severity of this metabolic bone disease by serum assays. In this cross-sectional study, we measured total and regional (head, arms, trunk, ribs, legs, spine and pelvis) bone mineral densities (BMD) by dual X-ray absorptiometry (DXA) in patients with variable degrees of CRF and correlated them with various bone markers. Decreased BMDs were detected in various skeletal sites (trunk and pelvis) in the patients' group. Total BMD Z score was lower in predialysis CRF patients than in the control subjects. Decreased BMD Z scores on weight-bearing bone were pronounced at L1 lumbar vertebra, femur trochanter, femur neck and Ward's triangle. Positive linear correlations were found between creatinine clearance and trunk, ribs, pelvis, and spine BMDs. There were inverse linear correlations between total BMD and total BMD Z score and alkaline phosphatase (AP), urine deoxypyridinoline (U-DPD) in the patients' group. There were no correlations between regional and total BMD, total BMD Z score and serum calcium, ionized calcium, and serum phosphate. There were inverse linear correlations between BUN, creatinine and bone-specific alkaline phosphatase in the predialysis CRF group. We evaluated the correlations between intact parathyroid hormone (i-PTH) and biochemical and other bone markers. There was statistically- significant linear correlation between i-PTH and AP. Other bone markers have no significant correlations with i-PTH. Our results demonstrated that there is significant bone loss in patients with CRF before the start of dialysis and also regional variations of BMDs in predialysis CRF patients. DXA is a useful method for evaluating regional and total BMDs and provides information about diverse regional skeletal changes. AP, i-PTH and U-DPD can predict BMD of predialysis CRF patients.

Key Words: Chronic renal failure, renal osteodystrophy, bone markers, bone mineral density

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Varieties of complications have been recognized in patients with chronic renal failure (CRF) (Eknoyan, 1986). Renal osteodystrophy has become a frequent complication in patients with terminal renal failure and various histologic forms such as osteitis fibrosa cystica, adynamic bone disease and mixed forms of both have been demonstrated (Malluche and Faugere, 1990). Osteitis fibrosa cystica represents the most frequent form, however

recent reports suggest that the prevalence of low turnover bone diseases has increased substantially (Sherrard *et al.* 1993; Fournier *et al.* 1994). The only reliable method for distinguishing patients with high turnover bone disease from those with low turnover adynamic bone disease is bone histomorphometric study of iliac crest bone biopsy after double tetracyclin labeling, but its clinical utility is restricted because the procedure is invasive, painful for the patient, unavailable in many hospitals, unsuitable for serial monitoring, problematic to assess regional variation in bone lesions, and difficult to perform routinely (Johnson *et al.* 1996). Because of its invasive nature, efforts have been made to predict indirectly, by serum assays, the type and severity of this metabolic bone disease. Immunoassayable intact parathyroid hormone (i-PTH) (Mazzaferro *et al.* 1990; Salusky *et al.* 1994), osteocalcin (Malluche *et al.* 1984; Mazzaferro *et al.* 1990), procollagen type 1 C-terminal extension peptide (P1CP) (Coen *et al.* 1992, 1993; Hamdy *et al.* 1994), bone-specific alkaline phosphatase (b-AP) (Urena *et al.* 1996) and urine deoxypyridinoline (Schmidt-Gayk *et al.* 1996; Vaccaro *et al.* 1996) represent the most recently used humoral markers of renal osteodystrophy. Also, measurement of bone mineral density is a reliable indicator of fracture risk in patients without renal disease (Wasnich *et al.* 1985) and may be a useful, noninvasive tool in detecting the early changes of renal osteodystrophy (Piraino *et al.* 1988; Ruedin *et al.* 1994). Dual X-ray absorptiometry (DXA) is a noninvasive method that quantifies total and regional bone mineral density (BMD) accurately and precisely (Johnston *et al.* 1991). Unfortunately, data on the usefulness of BMD and recently-developed biochemical markers in predialysis uremic patients are very limited. Most of the earlier studies in measuring BMD in renal osteodystrophy showed only trabecular or cortical bone changes, and there have been few reports on regional bone changes in renal osteodystrophy (Asaka *et al.* 1992; Chan *et al.* 1992; Gabay *et al.* 1993). In this study, we aimed to assess the utility of total and regional (head, arms, trunk, ribs, legs, spine and pelvis) BMD mesurements by DXA in patients with variable degrees of predialysis chronic renal failure and correlated the data with various biochemical markers for bone formation and resorption.

MATERIALS AND METHODS

Subjects

Twenty six predialysis CRF patients (13 males, 13 females) giving informed consent to participate in the study were recruited from our out-patient clinic. Mean age of the patient group was 53.4 years. In the patients' group, three males over 60 and six females in a postmenopausal state were excluded to compare absolute values of total and regional BMDs because of potential influence to BMD by age and menopausal status. Mean age of the patient group excluding the nine patients was 45.1 years. Thirty-one healthy control subjects (11 males, 20 females) were recruited from the health examination center for comparing BMD. Mean age of the control group was 40.6 years. Underlying renal diseases of the patients' group included chronic glomerulonephritis (N=10), diabetic nephropathy (N=8), hypertensive nephrosclerosis (N=2), and unknown (N=6). No patient had experienced bone fracture. Six of 13 females were postmenopausal. No patient had received corticosteroid 6 months prior to BMD measurement. The predominant phosphate binder used in the patients' group was $CaCO_3$.

Measurement of bone mineral density

BMD was measured by a Lunar DPX.L bone densitometer (version 1.3, Lunar, Madison, WI, USA) at the levels of whole body. Coefficients of variation in measuring BMD in the same subject was less than 1%. The results were expressed in absolute values and in standard deviations from the mean of age- and sex-matched normal subjects (Z-score).

Measurement of biochemical and various bone markers

Serum values of BUN, creatinine (CR), calcium (CA), phosphate (i-P), alkaline phosphatase

(AP) and albumin were measured on a Hitachi 747 autochemistry analyzer (Hitachi, Tokyo, Japan). Ionized calcium (i-CA) was determined using an ion-selective electrode (ICA2, Radiometer, Copenhagen NV, Denmark). Serum intact parathyroid hormone (i-PTH) level was measured by radioimmunoassay using antibodies directed against a mid-molecular epitope (intact PTH IRMA CT, Radim, Rome, Italy). Serum osteocalcin and procollagen type 1 C-terminal extension peptide (P1CP) were measured by enzymatic immuno-assay (EIA) using Novocalcin Kit (Metra Biosystems, Palo alto, CA, USA) and Prolagen-C kit (Metra Biosystems, USA) respectively. Bone-specific alkaline phosphatase (b-AP) was measured by Alkaphase kit (Metra Biosystems, Palo Alto, CA, USA). Urine deoxypyridinoline (U-DPD) was measured by Pirilinks-D kit (Metra Biosystems, Palo Alto, CA, USA).

Statistical analysis

Results are expressed as mean±SD. The relationship between BMD measurements and biochemical measurements was assessed using standard linear regression analysis. Differences between total and regional BMD were assessed by Student's t-test. Data analysis was performed using the software package SPSS PC+. The p value less than 0.05 was regarded as statistically significant for all analyses.

RESULTS

Trunk and pelvis BMDs were lower in the predialysis CRF patients than in the control (trunk: 0.903±0.095 g/cm^2 vs. 0.961±0.069 g/cm^2, p=0.02, pelvis: 1.037±0.139 g/cm^2 vs. 1.141±0.097 g/cm^2, p=0.004)(Table 1). Total BMD Z score (BMD-T-Z) was lower in predialysis CRF patients than in the control subjects (−0.064±1.024 vs. 0.578±0.841, P<0.05)(Fig. 1). Decreased BMD Z scores on weight-bearing bone were pronounced at L1 lumbar vertebra, femur trochanter, femur neck, and Ward's triangle in the patients' group (Fig. 1). There were inverse linear correlations between total BMD (BMD-T) and AP, i-PTH, and U-DPD in the predialysis CRF group (AP vs. BMD-T r=−0.5703, p=0.03, i-PTH vs. BMD-T r=−0.4066, p=0.044, U-DPD vs. BMD-T r=−0.4952, p=0.014). There were also inverse linear correlations between BMD-T-Z and AP, and U-DPD in the predialysis CRF group (AP vs. BMD-T-Z r=−0.4290, p=0.032, U-DPD vs. BMD-T-Z r=−0.4066, p=0.049). There were no correlations between regional and total BMD, BMD-T-Z and serum CA, i-CA, and i-P. Positive linear correlations were found between creatinine clearance (CCR) and trunk, ribs, pelvis, and spine BMDs (Table 2). We evaluated the correlations between renal function and various bone markers, and BMD. There were inverse linear correlations between BUN, CR, and b-AP in the predialysis CRF group (BUN vs. b-AP r=−0.4439, p=0.023, CR vs. b-AP r=−0.4180, p=0.034). There were no linear correlations between BUN, CR, and CCR and AP, i-PTH, P1CP, osteocalcin, and U-DPD in the same group (Table 3). We also evaluated the correlations between i-PTH and biochemical markers of bone. There were no correlations between i-PTH and serum CA, i-CA, and i-P in the predialysis CRF patients. There was statistically-significant linear correlation between i-PTH and AP. Other bone markers such as, b-AP, P1CP, osteocalcin, and U-DPD,

Table 1. Comparison of total and regional BMD between control and predialysis CRF patients

	Bone mineral density(g/cm^2)		p value
	Control	CRF	
Head	2.169±0.167	2.124±0.192	0.412
Arms	0.881±0.088	0.984±0.077	0.609
legs	1.173±0.092	1.136±0.128	0.251
Trunk	0.961±0.069	0.903±0.095	*0.020
Pelvis	1.141±0.097	1.037±0.139	*0.004
Ribs	0.703±0.058	0.688±0.070	0.440
Spine	1.227±0.112	1.171±0.149	0.155
Total	1.153±0.066	1.113±0.093	0.088

BMD: bone mineral density, CRF: chronic renal failure

Data are mean±SD.

*: p<0.05, compared to the control group

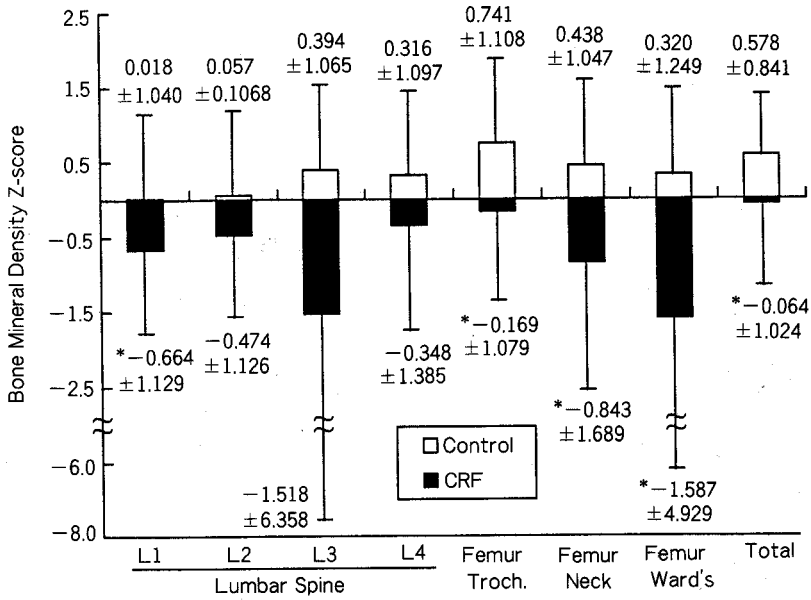

Fig. 1. *Comparison of total and weight-bearing bone mineral density Z-scores between the control and predialysis chronic renal failure patients.*
Troch: trochanter, Ward's: Ward's triangle,
CRF: chronic renal failure
Data are mean ± SD.
**: $p<0.05$, compared to the control group.*

Table 2. Correlation coefficients by linear regression of regional and total bone mineral densties and Z-scores on biochemical and various bone markers in patients with chronic renal failure

	Head	Arms	Legs	Trunk	Ribs	Pelvis	Spine	BMD-T	BMD-T-Z
AP	*−0.5065	*−0.5594	*−0.5169	*−0.4710	−0.3819	*−0.4655	*−0.4521	*−0.5703	*−0.4290
b-AP	−0.1543	−0.3794	−0.2498	−0.1883	−0.1179	−0.1788	−0.1622	−0.2865	−0.2121
i-PTH	*−0.4124	−0.3151	*−0.4214	*−0.4396	−0.3616	*−0.4678	−0.3556	*−0.4066	−0.2333
P1CP	0.0786	−0.0481	−0.0628	−0.1845	−0.1121	−0.1549	−0.2089	−0.1302	−0.2607
Osteocalcin	0.0996	−0.2572	−0.1513	−0.1085	−0.0546	−0.1379	0.0269	−0.1321	−0.1274
U-DPD	*−0.4342	−0.3941	*−0.4688	*−0.5229	*−0.4458	*−0.5076	*−0.5549	*−0.4952	*−0.4066
Ca	0.1615	−0.2643	−0.0761	−0.0496	−0.0644	−0.0423	−0.0546	−0.0632	0.1002
i-Ca	0.3631	0.0217	0.1192	0.1181	0.0502	0.1629	0.1641	0.1663	0.2526
i-P	−0.0013	0.2176	0.1074	−0.0032	−0.0425	−0.0562	−0.0366	0.0727	−0.2105
BUN	−0.0639	0.1776	0.1327	−0.0683	−0.0400	−0.0760	−0.0835	0.0432	−0.1261
CR	−0.0835	0.2091	0.0200	−0.1091	−0.1387	−0.1466	−0.0479	−0.0042	−0.2289
CCR	0.2733	0.1802	0.3711	*0.4270	*0.4321	*0.4289	*0.4205	0.3710	0.3776

BMD-T: total bone mineral density, BMD-T-Z: total bone mineral density Z-score, AP: total alkaline phosphatase, b-AP: bone specific alkaline phosphatase, i-PTH: intact parathyroid hormone, P1CP: procollagen type 1 c-terminal extension peptide, U-DPD: urine deoxypyridinoline, Ca: calcium, i-Ca: ionized calcium, i-P: inorganic phosphorus, BUN: blood urea nitrogen, CR: serum creatinine, CCR: creatinine clearance
*: $p<0.05$

Table 3. Correlation coefficients by linear regression of BUN, CR, and CCR on biochemical and various bone markers in patients with chronic renal failure

	BUN	CR	CCR
Alkaline phosphatase (total)	−0.3481	−0.2980	0.1054
Alkaline phosphatase (bone specific)	*−0.4439	*−0.4180	0.331
i-PTH	−0.2059	−0.0182	−0.2036
PICP	−0.1433	−0.0958	0.0613
Osteocalcin	−0.2108	0.0299	−0.1167
Urine deoxypyridinoline	−0.1482	−0.1272	−0.2265
Calcium	−0.3618	*−0.4307	0.2394
Ionized calcium	−0.2909	−0.2241	0.2317
Inorganic phosphorus	*0.6697	*0.8580	*−0.5995
Urine calcium	−0.2873	−0.2562	0.1327
Urine phosphorus	−0.3943	*−0.5464	*0.7973
Hemoglobin	−0.0787	−0.1388	0.1817
Hematocrit	−0.1118	−0.1370	0.1686

BUN: blood urea nitrogen, CR: creatinine, CCR: creatinine clearance, i-PTH: intact parathyroid hormone, PICP: procollagen type 1 c-terminal extension peptide

*: $p<0.05$

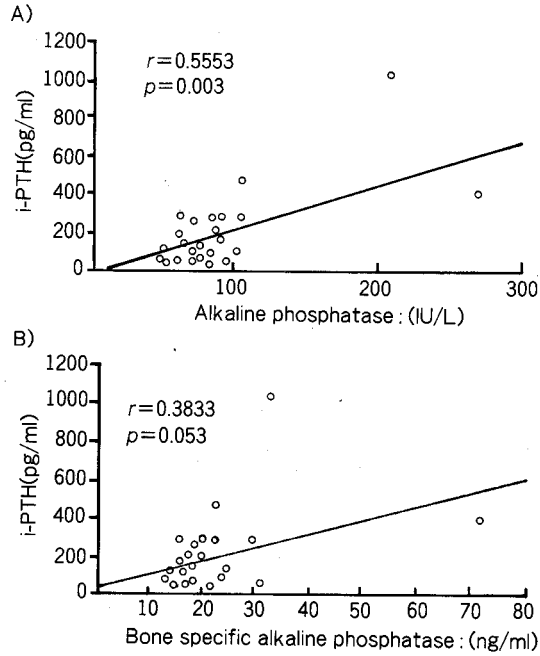

Fig. 2. *Correlation of total alkaline phosphatase(panel A) and bone specific alkaline phosphatase (panel B) with intact parathyroid hormone in predialysis chronic renal failure patients.*

Table 4. Correlation coefficients by linear regression of i-PTH on biochemical and various bone markers in patients with chronic renal failure

Bone markers	i-PTH	
	R	p value
Alkaline phosphatase (total)	0.5553	*0.003
Alkaline phosphatase (bone specific)	0.3833	0.053
PICP	−0.1540	0.452
Osteocalcin	0.3427	0.087
Urine deoxypyridinoline	0.2897	0.160
Calcium	−0.0874	0.671
Ionized calcium	−0.0326	0.898
Inorganic phosphorus	−0.0396	0.848

i-PTH: intact parathyroid hormone, PICP: procollagen type 1 c-terminal extension peptide

had no significant correlations with i-PTH (Table 4, Fig. 2).

DISCUSSION

Bone histomorphometric study is the gold standard of diagnosis of renal osteodystrophy (Couttenye *et al.* 1996). However, histological changes may vary in different parts of the skeleton and it may reflect only regional bone changes. In this cross-sectional study, we measured total and regional (head, arms, trunk, ribs, legs, spine and pelvis) BMD by DXA in patients with variable degrees of CRF and correlated it with various bone markers. Decreased BMDs were detected in various skeletal sites (trunk and pelvis) in the patients' group. BMD-T-Z was lower in predialysis CRF patients than in the control subjects. Decreased BMD Z scores on weight-bearing bones in the patients' group were pronounced

at L1 lumbar vertebra, femur trochanter, femur neck, and Ward's triangle. Gabay *et al.* (1993) showed decreased BMD at the lumbar spine, femoral shaft, and femoral neck in patients with end-stage renal failure present before the beginning of dialysis. These findings and our results confirm that there is significant bone loss in patients with CRF before the start of dialysis and there are also regional variations of bone density in predialysis CRF patients. Several authors previously reported that there were regional BMD changes in hemodialysis and CAPD patients. Chan *et al.* (1992) showed that patients with renal failure on hemodialysis had reduced bone densities as manifested by a reduction in total body, head, femoral trochanter, femoral neck, and Ward's triangle BMDs. Asaka *et al.* (1992) also reported that total body, trunk, pelvis, legs, and arms BMDs of hemodialysis patients were reduced significantly compared to the control subjects. These results and our observation confirm that bone loss is not uniform throughout the skeleton in patients with CRF. We also evaluated correlations of various biochemical and bone markers on BMDs. BMD-T and BMD-T-Z correlated inversely with AP and U-DPD in the patients' group. i-PTH also inversely correlated with some regional (head, legs, trunk, and pelvis) and total BMDs. Other parameters such as CA, i-CA, i-P, b-AP, PICP, and osteocalcin, were poorly correlated with BMDs. BMDs in CRF patients represented a composite of multiple abnormalities, including osteitis fibrosa cystica, osteomalacia, and adynamic bone disease. Piraino *et al.* (1988) reported that patients with bone biopsy-proven osteitis fibrosa cystica had increased BMD compared to normal, while those with low turnover bone disease had decreased BMD. Regional differences in individual BMD may depend on the predominant type of renal osteodystrophy and the fracture rate was twice as high in those patients with low turnover bone disease compared with those patients with osteitis fibrosa cystica. DXA is superior in detecting regional BMD changes compared to bone biopsy, which assesses bone content in a single skeletal site, but does not predict type of renal osteodystrophy. Total and regional BMDs generally cannot be predicted by any single biochemical parameters. Interestingly, AP, i-PTH, and U-DPD showed negative correlations with various regional and total BMDs and BMD-T-Z. Deoxypyridinoline, which is a component of bone collagen, is specific for bone degradation and is a good marker of bone resorption (Schmidt-Gayk *et al.* 1996). In our study, U-DPD showed good inverse correlation with regional (head, legs, trunk, ribs, pelvis, and spine) and total BMDs and BMD-T-Z. However, bone loss in predialysis CRF is the result of multiple abnormalities and thus cannot be predicted by one single bone marker. Renal function parameters, such as BUN, CR, and CCR, have no direct correlations with various bone markers except b-AP in the predialysis CRF group. Some part of the skeleton such as trunk, ribs, pelvis, and spine BMDs correlated well with renal function parameters. This result also suggests that no uniform bone changes occur in predialysis CRF patients. We also evaluated the correlation between i-PTH and other bone markers. There was statistically significant linear correlation between i-PTH and AP. Other bone markers such as b-AP, PICP, osteocalcin, and U-DPD had no significant correlations with i-PTH. Urena *et al.* (1996) reported in 42 hemodialysis patients that there were good linear correlations between i-PTH, AP and b-AP. Correlation between i-PTH and b-AP in our case is also linear, but statistical power is marginal ($p=0.053$).

In summary, there is significant bone loss in patients with CRF before the start of dialysis and there are also regional variations of BMD in predialysis CRF patients. DXA is a useful method for evaluating regional and total BMDs and provides information about diverse regional skeletal changes, which cannot be obtained by bone histomorphometry. Various bone and biochemical markers do not predict BMD of predialysis CRF patients except AP, i-PTH, and U-DPD. Therefore, optimal monitoring of renal bone disease in predialysis CRF patients still must rely on a combination of clinical, radiological, biochemical, and histological assessment.

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